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VOLUME VII NUMBER 11

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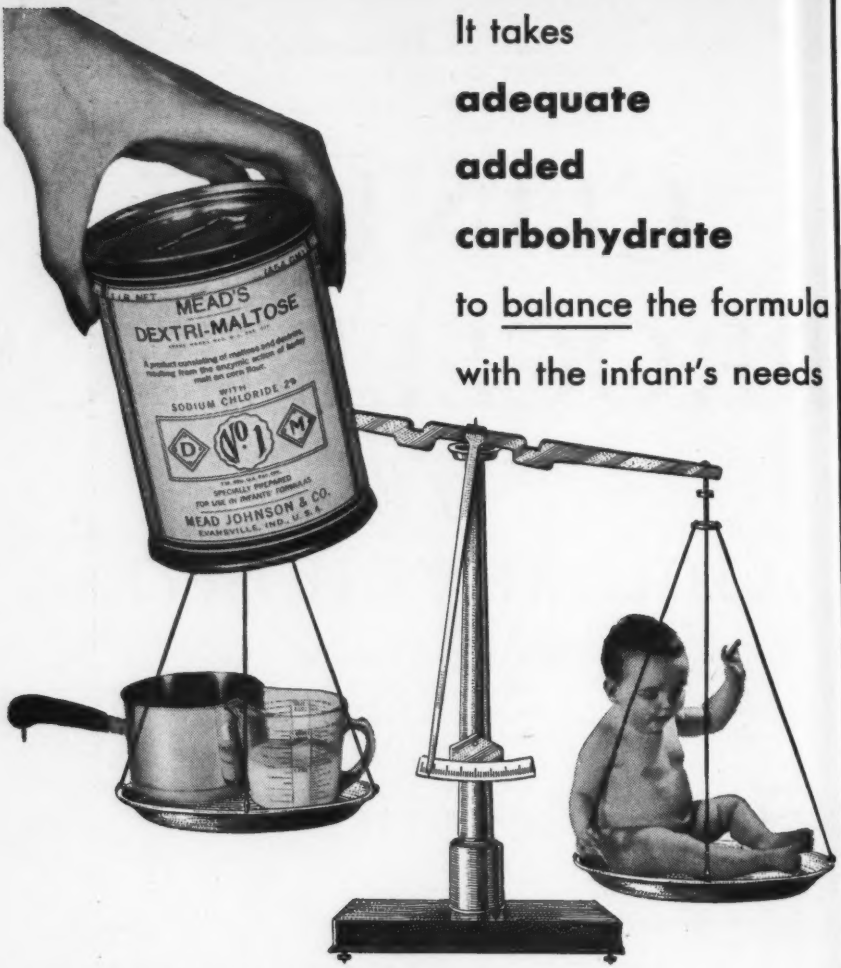

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CLINICAL PROCEEDINGS

OF THE CHILDRENS HOSPITAL

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CONTENTS

FEELING THE PYLORIC TUMOR. *Gordon W. Daisley, Jr., M.D.* 263

INTRACEREBRAL ABSCESS: A TEN YEAR REVIEW. *Hubert L. Reid, M.D. and Robert H. Parrott, M.D.* 264

HEMOLYTIC JAUNDICE FOLLOWING COMBINATION SULFADIAZINE-PENICILLIN THERAPY. *Stanley I. Wolf, M.D.* 275

DIABETIC COMA WITH MARKED HYPERGLYCEMIA IN INFANCY. *Dan Feriozi, M.D.; E. Clarence Rice, M.D., and John A. Washington, M.D.* 279

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FEELING THE PYLORIC TUMOR

Editorial

Gordon W. Daisley, Jr., M. D.

The diagnosis of congenital hypertrophic pyloric stenosis is a relatively simple one, and the pathognomonic sign is palpation of the olive-shaped tumor. Often, however, while the usual diagnostic signs are in evidence, it is sometimes difficult to actually feel the mass. Many methods and techniques for palpation have been described, and most all emphasize that an unhurried examination is necessary. Even then, palpation may be equivocal or may fail to be confirmatory. In many instances, barium studies are performed when palpation fails.

It has been my observation that the pyloric tumor can be felt easily and quickly, even in a struggling and crying infant, when the procedure outlined below is followed:

1. Place the infant flat on his back with his right side toward the examiner.
2. Place the *dorsum* of the right hand (palm upward) on the lower abdomen with the finger tips approximately at the level of the umbilicus.
3. With the left hand behind the neck, jacknife the baby over the examining hand, and with an upward and inward motion, feel for the mass.

I can only postulate why this simple method has been so successful; it would seem that the resistance of the rectus muscle is overcome in this position; and, perhaps, the liver falls forward and away from the tumor, leaving it readily accessible to the exploring finger tips.

Whatever the reason, it is hoped that this method of palpation will help practitioners when the conventional techniques fail to disclose the mass.

INTRACEREBRAL ABSCESS

A Ten Year Review

Special Report No. 215

Hubert L. Ried, M. D.
Robert H. Parrott, M. D.

INTRODUCTION

Although the incidence and management of cases of brain abscess have altered considerably with the advent of antibiotics, chemotherapy, and improved neurosurgical techniques, the number of published reports on this disease entity is relatively few. This is true especially of the pediatric age group. The authors have been unable to locate a more recent review of brain abscess in the first decade of life than Holt's[1] monograph published in 1898. For these reasons, it was thought that a review of the cases admitted to a pediatric hospital and a comparison with other similar reports would be worthwhile.

Intracranial abscesses may be classified as subdural, subarachnoid, intraventricular, or intracerebral[2]. This report discusses only the intracerebral type, and includes all patients with the diagnosis of brain abscess who were admitted to the Children's Hospital, Washington, D. C. in the ten-year period from 1940 through 1950. As the range of children hospitalized here includes birth through twelve years, this study necessarily is limited to individuals in that age group. The clinical records, operative notes, and autopsy protocols were available for study in each instance. During this ten-year period, thirteen cases of brain abscess were hospitalized.

INCIDENCE

The majority of reports indicate that brain abscess is rare in the first decade of life, the fastigium occurring from ten to thirty-five years of age. According to Grant,[3] 12 per cent of brain abscess occurs during the first decade of life, 57 per cent within the second and third decades, 15 per cent during the fourth decade, and 16 per cent after the fiftieth year. The ages of patients in our study ranged from 1 month to 12 years. Of the 13 patients studied, 8 were under 6 years, and 5 were from 6 to 12 years of age. Three cases occurred in infants under 1 year of age and the youngest was 1 month old. In a review of the literature, we were unable to find a reported case of brain abscess in an infant younger than this patient. Sanford,[4] in 1929, reported nineteen original and collected cases of brain abscess in infants under 12 months. The youngest child in his series was 6 weeks old The average age of the children in our report was 4.9 years. Grant[3] states

that males are apparently more subject to brain abscess than females. In our review, the males outnumbered females 9 to 4. Ten of the patients were white and three colored.

PATHOGENESIS

There are four routes by which infection can reach the brain:[3] 1. by direct implantation, 2. by contiguous spread, 3. by metastatic extension (hematogenous), and 4. by undetermined pathways from unknown sources.

Trauma is rarely the cause of brain abscess unless the dura is penetrated. Bullet or shrapnel fragments, depressed fractures, and stab wounds may provide the portal of entry. It is possible, too, that the surgeon's knife or the diagnostic or aspirating needle may carry sepsis to the cerebrum.

CHART 1

Age Incidence

Years	*Number*
1	3
1–6	5
6–12	5

The most common focus of a brain abscess is a contiguous infection. Otitis media, mastoiditis, and paranasal sinusitis are the usual primary foci. Potential, but less common, sources are infections of the orbit; cavernous or lateral sinus thromboses; meningitis; furunculosis; infections of the face, neck, and scalp; and osteomyelitis of the skull.

The organisms from these areas may reach the brain in four ways.

1. Spread across the meninges. Unless there be an accompanying meningitis, this method of spread would presuppose the formation of adhesions between the dura, arachnoid, and pia which would cause a block of the subarachnoid space.

2. Spread along the perivascular spaces.

3. Retrograde infected thromboses of veins or arteries. In this connection, the possibilities for communication among the systemic veins, the diploic veins, dural sinuses, and the cerebral vessels should be kept in mind. By such pathways, an abscess might form in a site not directly adjacent to the primary pathology.

4. Performed pathways, e.g. nerve sheaths, foramina, the labyrinth, or internal auditory meatus.

A combination of these methods is responsible for the spread of infection in many instances.

Septicemia from a distant primary focus of infection may cause a brain abscess. In such cases approximately 50 per cent of the initial lesions are

intrathoracic. The most common original lung pathology is chronic bronchiectasis. Empyema, lung abscess, tuberculosis or actinomycosis may be the primary disease. Bacterial endocarditis, amebic dysentery, tonsillitis, tonsillectomy, dental infections, and exodontia have been recorded as predisposing causes for hematogenous brain abscesses. An interesting observation made in recent years is the high incidence of brain abscess in persons with congenital heart lesions which permit a shunt of the pulmonary circulation by blood returning from the systemic veins.

In the 13 patients reviewed, 4 (30 per cent) of the abscesses were preceded by infections of the middle ear. In 2 children (15 per cent), the focus was an upper respiratory infection, the extent of which was not noted on the clinical records; and 2 patients (15 per cent) developed brain abscess during the course of purulent meningitides. Congenital heart disease

CHART 2

Predisposing Causes

Direct	1	
Trauma		1
Contiguous	6	
Middle Ear Infection		4
Meningitis		2
Hematogenous	4	
Upper Respiratory Infection (?)		2
Tonsillectomy		1
Tetralogy of Fallot		1
Combination	1	
Intercranial Hemorrhage Plus Impetigo		1
Unknown	1	

(tetralogy of fallot) and trauma were associated with 1 case each (7 per cent). One patient had undergone a tonsillectomy ten days prior to hospitalization. The 2 remaining patients were a 6-week old infant who had an intracranial hemorrhage at birth followed by impetigo; and a 1-month old infant who had been admitted at 6 days of age for an episode of cyanosis, the etiology of which was never determined.

In Evans' series[5] of 194 patients with brain abscess, trauma accounted for 8 (4.1 per cent); contiguous spread for 122 (63 per cent); and hematogenous spread for 64 (24 per cent) of the cases. Alpers[6] writes that 4–5 per cent are traumatic in origin, 40–60 per cent are secondary to otitis media or sinusitis, and from 2–24 per cent are metastatic. The causes of brain abscess in the infants in Sanford's series[4] was found to be: trauma or birth injury—21 per cent, otitis—31 per cent, other infections—10 per cent and spina bifida—5 per cent.

With respect to the incidence of brain abscess in association with congenital heart disease of the arterio-venous shunt-type, Marondi[7] reviewed autopsy protocols and found eleven acceptable examples of this combination of pathology among 3,338 autopsies. These eleven patients were over 2 years of age at death. Four out of five cases of tetrology of Fallot, two out of three cases of associated intraventricular and intra-auricular septal defects, and five out of eleven cases of isolated intraventricular septal defects were associated with brain abscess.

CHART 3

Pathogenesis

	EVANS	ALPERS	CHILDREN'S HOSPITAL
	%	%	%
Direct	4.1	4–5	15
Contiguous	63	40–60	46
Hematogenous	43	2–24	31
Unknown			8

ETIOLOGY

Any potentially pathogenic organism may cause an abscess when implanted in the brain. The most common offenders are *Streptococcus hemolyticus*, *Staphylococcus aureus*, and *Diplococcus pneumoniae*. Other organisms which have been recovered from brain abscesses include *Escherichia coli*, *Salmonella typhosa*, *Bacillus pyocyaneus*, *Hemophilus influenzae*, *Proteus vulgaris*, *Clostridium welchii*, *Actinomyces bovis*, and *Endameba histolytica*. Sanford[4] discovered that the causative organism in the infantile brain abscess in his series was staphylococcus in 90 per cent of cases cultured.

At Children's Hospital, Washington, D. C., the etiological agent was isolated in eleven (85 per cent) of the thirteen cases. In seven instances, (53 per cent) a streptococcus was the causative agent. Four cases yielded hemolytic streptococcus, three yielded non-hemolytic streptococcus, and one case showed an anaerobic streptococcal organism. The remaining causative bacteria were *Staphylococcus albus*, *Escherichia intermedius*, *Hemophilus influenzae*, Type B and *Diplococcus pneumoniae*. The latter two organisms were also identified as causative agents of a concurrent meningitis.

PATHOLOGY

Once having implanted in cerebral tissue, the responsible organism initiates a series of processes which have been well summarized by Carmichael et al[8] as:

1. Focal necrosis.

2. Primary delimitation.
3. Secondary delimitation.
4. Repair, vascularization.

In the second and third of these stages, attempts at encapsulation are made by a proliferation of fibroelastic tissue whose origin is either from local blood vessels or from lymphocytes in the area. In the fourth stage four layers may be found: central necrosis, a revascularizing granulomatous border, a zone of hyperemia and fibrosis, and a zone of gliosis. The outer zones represent encapsulation of the infection. An understanding of this concept is essential for any rational management of brain abscess. Not all abscesses become encapsulated, nor is the time for complete encapsulation well known. Anaerobic bacteria do not favor the fibrous enclosure; while aerobic bacteria, especially the cocci, tend to aid it. The virulence of the organism, the resistance of the host, and other factors such as the presence or absence of sepsis, play a large role in the degree of encapsulation. If encapsulation is to take place, it usually will be complete in about three weeks. The autopsy or surgical reports on our cases recorded the presence of a capsule in five instances. The shortest period of time between onset of symptoms and discovery of a capsule was two weeks. Three showed an interval of three weeks and one, an interval of five weeks.

The most common sites of brain abscess are the temporal lobes, the cerebellum, and the frontal lobes. The abscess usually occurs homolateral with the primary infection, although a contralateral involvement is possible. An abscess will localize more frequently in the temporal lobe than in any other because of its proximity to the most common foci, i.e., the middle ear and mastoid. There is a correlation between the source of infection and the location of the abscess. Most abscesses secondary to otitis or mastoiditis occur in the temporo-sphenoidal lobes. Those secondary to paranasal sinus infection occur in the frontal lobes. Those due to septicemia localize in the anterior cerebrum. Lateral sinus thrombosis and otitis may precede a cerebellar abscess. Abscesses may be single or multiple depending upon the source of infection and degrees of loculation. According to Tutton,[2] 50 per cent of abscesses become loculated in the frontal and cerebellar areas.

At Children's Hospital, the location of intracerebral abscesses varied greatly, and did not correspond so closely with the source of infection as one might predict from other series. Four of them were located in the frontal or fronto-parietal region. Two were located in the parietal area, and two in the temporal lobes. The occipital lobe and cerebellum were involved in one case each. One massive abscess involved the temporal, parietal, and occipital lobes. In three patients, multiple abscesses were encountered and in two of these, the occipital lobes and cerebellum were involved. In the third instance, the abscesses were confined to the temporal lobe. Of the

thirteen cases reported, the abscess or abscesses were found on the left side in eight (61 per cent) patients. None were found in the midline.

CHART 4

Location of Abscess

Frontal; Fronto-Parietal	4
Parietal	2
Temporal	2
Occipital	1
Cerebellar	1
Temporo-Parieto-Occipital (massive)	1
Occipital-Cerebral	2

CHART 5

Presenting Symptoms and Signs

Drowsiness	8	Stiff neck	7
Headache	6	Reflex Changes	7
Fever	6	Fundal Changes	7
Vomiting	5	Paralysis	5
Cyanosis	1	Convulsions	3
Convulsions	1	Ataxia	2
Coma	1	Full Fontanel	2
		Suture Separation	2

SIGNS, SYMPTOMS, AND DIAGNOSIS

Typically, the signs and symptoms of brain abscess are those of the source of infection, if still present; those of increased intracranial pressure; and localizing signs due to the abscess itself. In our series, the duration of time from the onset of symptoms to hospitalization ranged from 1 to 35 days, with an average of 12.6 days.

There was a marked variation in the presenting symptomatology of these patients. The most common complaints were drowsiness and lethargy. Other symptoms encountered in order of frequency were headache, fever, vomiting, cyanosis, convulsions and coma.

Similarly a variety of findings were noted on physical examination. These findings in order of frequency were: stiffness of the neck; abnormal reflex changes, e.g., Kernig's, Brudzinski's, and Babinski's, signs; fundoscopic changes, e.g., congestion of retinal vessels, papilledema; paralysis; reflex changes; convulsions; ataxia; bulging fontanel; tremors; alteration in blood pressure; and separation of cranial sutures.

For the most part the cases reported correspond with the usual picture of

increased intracranial pressure as listed by Grant.[3] He points to the following features as helpful in the diagnosis:

1. A history of infection.
2. Headache which may be very intense and may localize over the site of the abscess.
3. Retardation of mental processes or "muddied" intellect.
4. Nausea and vomiting.
5. Papilledema.

The latter finding occurs in about 50 per cent of brain abscesses and is more apt to be present when the mass is encapsulated.

Several features said to indicate increased intracranial pressure—which are not fully corroborated in the present series are:

1. Subnormal temperature: nine of our patients had *fever* (minimum 101.0 F) at some time during their hospital stay.
2. Slowed pulse and respirations: only three of our cases showed relative bradycardia and only one patient had any degree of slowed respirations.

Whether the temperature elevation present in most instances invalidated pulse rate and respirations as symptoms is difficult to say. In five instances, symptoms or signs were present on admission or shortly thereafter which allowed accurate localization of the lesions. Some of these signs are those already recorded as present on the initial examination.

Localization of a brain abscess may be possible if the primary source of infection is evident, e.g., ear infection predisposes to temporo-spenoidal abscess; sinusitis to frontal abscess; ear infection and sinus thrombosis or labyrinthitis to cerebellar abscess. A traumatic abscess may be localized by its proximity to the original skull wound. Hematogenous abscesses are rarely cerebellar and usually occur in the anterior cerebrum. In the presence of increased intracranial pressure, suspicion of temporal lobe abscess is heightened by a history of chronic or acute ear infection, pain on percussion of the involved area, an opposite central facial nerve weakness, paresis of the opposite arm, contralateral Babinski's sign, and contralateral homonymous hemianopsia. Frontal abscess may present ipsilateral exophthalmos, chemosis and palpebral edema, frontal headache, personality changes, motor aphasias, abducens and oculomotor nerve palsies, pupillary irregularity, contralateral central facial and arm weakness and contralateral Babinski's sign. Cerebellar abscesses may be identified by the presence of horizontal slow nystagmus, falling to the affected side, a pointing error with the homolateral arm, ataxia, and adiadokokinesia.

DIAGNOSIS

Most authorities agree that lumbar puncture is of aid in the diagnosis with the warning that it be performed with caution in suspected cases of

cerebral abscess. Traditionally, the pressure is said to be elevated, the protein elevated, the sugar normal and the leukocyte count normal or slightly elevated unless the disease is complicated by meningitis. Usually no organism is cultured from the cerebrospinal fluid.

Our findings are at some variance with these features, especially as regards protein content. Lumbar punctures were performed in 11 of the 13 patients on admission and the pressure recorded in five instances. The cerebrospinal fluid pressure was normal in 2 cases and elevated in three (300, 360, and 600 millimeters of water, respectively). The pressure was observed to be grossly increased in one case but was not measured. A pleocytosis was recorded in nine of the twelve cases having lumbar puncture. In these patients, the count ranged from 14 white cells to 28,300 per cubic millimeter. The two cases associated with a frank purulent meningitis showed remarkably high counts, namely, 20,000 cells per cubic millimeter and 28,300 cells per cubic millimeter. The remainder of the cell counts ranged from 14 cells to 540 cells per cubic millimeter. In all but one instance the cells were predominantly polymorphonuclears. With the exception of the cases which were associated with a frank purulent meningitis, only one case was found to exhibit an elevated protein content. This was 200 milligrams per cent. The sugar content of the spinal fluid was essentially normal in all cases except those in which a meningitis preceded the abscess formation. In these two cases, the sugar was significantly decreased. Spinal fluid smears and cultures were negative in ten of the thirteen cases. The two cases of brain abscess developing during the course of purulent meningitis produced positive spinal fluid cultures for *H. influenzae* and *D. pneumoniae*.

A note of explanation should be made concerning the patients who did not receive lumbar punctures on admission to the hospital. In one patient, a one-month old infant, attempts at lumbar puncture were unsuccessful. A ventricular puncture was performed and frank pus was obtained. In retrospect, after autopsy findings were known, the needle was probably inserted directly into the abscess itself. In the remaining case, which followed trauma, surgery was undertaken immediately after admission and a lumbar puncture performed after operation revealed xanthochromic fluid. Blood cultures were taken in five of the thirteen patients. In three of these a pathogenic organism was isolated, viz., *Staphylococcus albus*, *Streptococcus hemolyticus*, and *Diplococcus pneumoniae*.

Peripheral blood counts are of little significance. White blood counts were performed on admission in twelve of the thirteen patients reviewed. In ten instances, a leukocytosis with a predominance of polymorphonuclear cells was seen. The white blood count of these patients ranged from 11,000 to 30,100 per cubic millimeter. In the remaining two patients the count

was 5,600 and 7,200 respectively. However, in these two cases there was a shift to the left in the Schilling index. Urinalyses were essentially normal.

Further aids to diagnosis are skull x-rays, ventriculograms, and electroencephalograms. A flat x-ray of the skull occasionally may reveal gas within an abscess or may show the primary pathology if there is osseous involvement. Ventriculography may be necessary to localize a process infringing upon the ventricular cavities. Electro-encephalography may reveal a "slow" focus over the site of an abscess. Cerebral arteriography has been employed but is not felt by most workers to be of great value in localizing an abscess.

Skull x-rays were recorded in five patients. One showed the depressed fracture which was the portal of entry for abscess formation. X-rays of two of the remaining revealed an increase of intracranial pressure and two were normal in appearance. Ventriculograms were performed on five patients.

CHART 6

Differential Diagnosis of Brain Abscess (from Alpers)

	BRAIN ABSCESS	TUMOR	MENINGITIS	THROMBOSIS	LABYRINTHITIS
Onset	Acute-Chronic	Chronic	Acute	Acute	Acute
History of infection	+	−	+	+	+−
Headache	+−	+−	+	+	+−
Choked Disc	+	+	+	+	−
Pulse	Slowed	N	Fast	Fast	N
Mental State	Befuddled	Occasionally Befuddled	N	N	N

In all instances there was evidence of a space-occupying mass. The localization by ventriculograms was corroborated by surgery. Electroencephalographic study was not available in any of our patients.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of brain abscess includes all of the causes of increased intracranial pressure, localizing neurologic signs, convulsions, or disturbed equilibration. Brain tumor, acute meningitis, lateral sinus thrombosis and labyrinthitis are prominent among such conditions. Alpers[6] has published a useful table for differential diagnosis. The most common admitting diagnosis was meningitis. This was the initial impression in five instances. Brain abscess was noted as a possibility in two of these children. In two instances, the admitting diagnosis of brain abscess was correct. In two instances, brain tumor was suggested as an admitting diagnosis. Other diagnostic possibilities considered were: poliomyelitis, encephalitis,

pneumonia, embolism, laceration of brain with meningoencephalitis. The correct diagnosis of cerebral abscess was made at admission in two cases (14 per cent), although in two others (14 per cent) the correct impression was included in combination with other diagnoses. In one instance, the patient had been hospitalized one month previously with a history of vomiting, headaches, and pain in the eye. After a stay of two days the child was discharged with a diagnosis of hysteria. Before death or surgery a diagnosis of brain abscess or accurate localization of a mass was accomplished in seven cases (54 per cent).

TREATMENT

According to Oliver and Leese[9] the methods available in the treatment of brain abscess are:

1. "Delayed excision after a capsule has had time to form, life being maintained by penicillin-replacement therapy and sometimes also by decompression. The object is to encourage the formation of a thick capsule.
2. "Immediate radical excision as soon as the diagnosis has been made.
3. "Aspiration and penicillin replacement without excision; begun as soon as the diagnosis is made and repeated when necessary without delay."

These authors concede that there is no single method which can be successfully utilized in the treatment of all brain abscesses, and that treatment of a particular case must be individualized. However, they feel that, when possible, the preferred method of treatment is aspiration and penicillin-replacement therapy without excision except in cases in which the patient does not improve or follows a downhill course. In these instances the capsule of the abscess is thick and acting as a "tumor", or a multilocular abscess is present. Total removal of the abscess is then a necessity. Using this method of therapy, these investigators had only one death in eight cases of brain abscess. Haynes[10] also stresses the need for individualization in the mode of therapy. However, he emphasizes the importance of the degree of encapsulation and the necessity of "removing every bit of the capsule before an abscess can be considered cured." Both of these authors stress the importance of parenteral antibiotic therapy. In addition, Haynes[10] highly recommends sulfadiazine administration.

Treatment of the patients included in this report consisted of penicillin parenterally and sulfonamides in eight patients (61 per cent). Of these patients five underwent surgery. Three (23 per cent) were treated with sulfonamides. Of these three patients, one underwent surgery. Two patients (15 per cent) received parenteral fluids alone. Surgical treatment of the six cases consisted of aspiration of the abscess cavity followed by irrigation

with saline solution. Instillation of penicillin into the abscess cavity was used in five of the six cases. In no instance was the abscess excised with the capsule. In one case, a second procedure was contemplated to remove the abscess capsule, but response to previous surgery and antibiotics and chemotherapy was satisfactory, and no further intervention was deemed necessary. In another case, complete excision was contemplated, but the abscess was too massive to accomplish this.

PROGNOSIS

With adequate means at hand for control of acute infections, especially of the ear, the incidence of brain abscess can be expected to diminish. Likewise, more and more case reports of successfully-treated brain abscess are appearing in the literature. While our records are inconclusive as to the relative incidence of brain abscess since the advent and use of antibiotics, they do tend to show a greater measure of success in treatment in recent years. Four of the thirteen cases described are living. One is considered to be recovered. One has hemiparesis and convulsions, which are well controlled by the use of dilantin. One has had recurrent convulsions. The fourth patient, when last seen in 1949, had a hemiparesis. There was one patient in the series who survived surgical drainage of the abscess only to die two months later because of hydrocephalus and malnutrition. From 1940 to 1943, the mortality rate was 100 per cent; from 1944 to 1947 it was 66 per cent; from 1948 through 1950, 57 per cent.

CHART 7

YEAR	MORTALITY	NUMBER OF CASES
	%	
1940–43	100	3
1944–46	66	3
1948–50	58	7

SUMMARY

1. The case records of intracerebral abscess at Children's Hospital from 1940 to 1950 are reviewed. Thirteen confirmed cases of the lesion are included.

2. Comparison of data is made with the available literature on brain abscess.

3. These data are in essential agreement except that, in the patients reviewed, there was no constant finding of bradycardia and slow respirations, low temperature, or elevated spinal fluid protein, all of which are

traditionally described as present in cases of brain abscess. We were unable to show a correlation between the source of infection and the location of the abscess.

4. Neurological data allowed localization of the mass in five or 38 per cent of the cases; ventriculogram localized the lesion accurately in all cases where it was performed.

5. Seven or 5 per cent of the cases were diagnosed accurately before death or surgery.

6. Four of the patients are living; three of these show neurological sequellae. The living patients are those who received treatment after 1945.

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HEMOLYTIC JAUNDICE FOLLOWING COMBINATION SULFADIAZINE-PENICILLIN THERAPY

Case Report No. 216

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M. M.*, a twenty-two month old white male was admitted to Children's Hospital in July 1951 with a history of fever and jaundice of four days' duration. He had been perfectly well until four days before admission when anorexia, lethargy, and fever of 103.0 F. were noted. The following day a diagnosis of pharyngitis was made. The patient was given an intramuscular injection of penicillin and a combination of sulfadiazine and oral penicillin to be taken four times daily was prescribed. The symptoms persisted despite this therapy. On the day preceding admission, the patient's temperature reached 105.0 F. and a mild febrile convulsion occurred. That evening, aureomycin and aspirin were added to the therapy, and shortly thereafter, persistent vomiting and anuria became manifest. On the morning of admission, another febrile convulsion occurred and an icteric tinge to the skin and sclerae was noted. He was then hospitalized for diagnosis and treatment.

The past medical history revealed no previous illnesses and no exposure to con-

* This patient admitted on the private service of Drs. Warren G. Preisser and Joseph M. LoPresti.

tagious disease. Family history was also negative for familial diseases including evidence of bleeding tendencies or blood dyscrasias.

Systemic review was essentially negative. The stools were of normal color during the present illness. There had been no urinary symptoms until eighteen hours before admission when anuria developed.

Admission physical examination revealed a well developed white male infant lying in bed appearing quite ill. He was breathing rapidly with flaring of the alae nasi, but no retraction of the sternum was noted. He was quite lethargic. The skin was pale and slightly icteric in color. The sclerae were definitely icteric. The temperature was 101.6 F.; the blood pressure, 130/80; and the pulse and respirations, rapid. The throat and both ear drums were slightly infected. There was some resistance in the right upper quadrant, but the liver edge was not definitely palpable. The spleen was not palpable. There were a few small, purpuric lesions on the back, chest, upper arms, and legs.

Shortly after admission the patient voided a large amount of dark red, frankly bloody urine and continued to do so for the first twenty hours in the hospital. A non-bloody specimen examined on the second hospital day revealed 500 milligrams of albumin and 1 to 2 white blood cells per high power field. The urine was never bloody following the first day in the hospital and was reported negative for bile and urobilinogen. The carbon dioxide combining power on admission was 33 volumes per cent. This was corrected with M/6 lactate solution intravenously. Throat culture on admission revealed micrococci. Admission blood count revealed hemoglobin, 9.5 grams; red blood cells, 2,600,000; white blood cells, 6,300 with 27 segmented cells, 37 bands, 35 lymphocytes, and 1 eosinophile per 100 cells. Van den Bergh showed a total of 0.77 milligrams per cent of bilirubin, 0.74 milligrams of which was indirect. Roentgenographic examination of the chest was negative. Other laboratory work in the hospital included: a fragility test which was normal; a positive Coombs test, a Donath-Landsteiner cold agglutination test which was negative, and a normal platelet count.

The patient's course in the hospital was uneventful. He was treated with penicillin and whole blood. A total of 900 milliliters of blood was administered. The jaundice disappeared on the third hospital day. The blood count rose daily and on discharge, the hemoglobin was 11 grams and the red blood cells numbered 4,700,000. The child was alert, friendly, and of a healthy color. The diagnosis on discharge was secondary hemolytic anemia, probably due to sulfa drug reaction.

DISCUSSION

There are many cases of hemolytic jaundice due to sulfa drugs reported in the literature. The purpose of this report is to reemphasize the toxic manifestations of the sulfa preparations and to condemn the use of multiple drugs as so-called "shot-gun" therapy in conditions that will respond equally well to any single drug or antibiotic.

Fink and Smith[1] listed the following untoward reactions to sulfonamide drugs and their usual time of onset:

1. Gastro-intestinal: nausea and vomiting (1st to 2nd day of admission).
2. Renal: hematuria, oliguria, anuria (1st week).
   A. Mechanical obstruction by crystals.
   B. Toxic.

3. Neurologic: mental disturbances (1st to 2nd day).
4. Blood and blood-forming organs: leukopenia, anemia, hemolytic anemia, jaundice, purpura (1st to 2nd week).
5. Systemic: fever with or without rash occurring alone or in combination with any of the above reactions.
   A. Initial administration: fever with or without rash (5th to 9th day).
   B. Subsequent administration: fever usually with rash (1st 24 hours).

In their report, Fink and Smith reported two cases of hemolytic anemia in a survey of five thousand cases, both accompanied by fever and jaundice and one accompanied by purpura. Symptoms began on the second and third days of drug administration respectively. These cases were identical with the case presented.

The mechanism of production of hemolytic reactions has caused much speculation. Damashek[2] reported three cases of hemolytic anemia following sulfa drug administration in which cold isohemagglutinins and autohemagglutinins were present. Although the cold agglutination test was negative in our case, the positive Coombs test did indicate the presence of abnormal agglutinins in the patient's serum. Damashek has demonstrated[3] that agglutinins injure the red blood cell membrane making it susceptible to hemolysis by trauma and stasis. This erythrostasis and subsequent hemolysis may well be due to agglutination of the red blood cells. He also postulates that sulfonamide drugs may act to alter the patient's red blood cells so as to serve as an antigen with the subsequent formation of an agglutinating antibody. Whatever the actual mechanism of hemolysis may be, it has definitely been demonstrated that abnormal agglutinins are to be found in the serum in patients with hemolytic anemia due to administration of sulfa drugs.[4]

The anemia due to sulfonamide toxicity is thought to be purely peripheral by most observers[5] and this is borne out by the usual finding of hyperplasia of erythropoietic elements in the bone marrow in such cases.[6, 7]

It is important to emphasize at this point that the toxic manifestations due to sulfonamide administration are not related to the amount of sulfa drug administered and are likely to recur if the drug is administered again. This was proven by Long, Bliss and Feinstone[8] who readministered sulfanilamide to four persons who had previously developed acute hemolytic anemia following administration of this drug. In three of these cases, anemia developed after a few days—on the identical day on which the anemia had been previously noted. Carrol[9] stressed the importance of this toxicity in his discussion of sulfonamide combinations. He presented a case of toxicity from one of the sulfa drugs in a proprietary multi-sulfa preparation. He stated that the use of triple sulfa preparations might theoretically increase the incidence of toxic reactions such as rashes, fevers, neutropenias, and

hemolytic anemias which are not dependent on dosage but on sensitivity to a specific drug. It is not the purpose of this report to discuss the advantages or disadvantages of multiple sulfa drug preparations, but it is to be emphasized that the more individual drugs introduced in therapy of a specific infection, the greater the possibility of toxic reactions. Since combination penicillin-sulfa preparations are used so very often to treat infections that would respond adequately to either drug, it is incumbent upon physicians to evaluate each infection as to the probable pathogen responsible and the drug best suited to handle this infection. The use of "shot-gun" therapy to treat a fever with no regard to the specific infection is to be condemned.

SUMMARY

1. A classical case of acute hemolytic anemia probably secondary to sulfonamide administration has been presented.

2. The toxic reactions from sulfonamide administration and the probable mechanism of production of hemolytic reactions are presented and briefly discussed.

3. Arguments against the use of multi-sulfa and multi-antibiotic combinations are presented with a condemnation of so called "shot-gun" therapy.

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DIABETIC COMA WITH MARKED HYPERGLYCEMIA IN INFANCY

Case Report No. 217

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Because of the infrequency of associated degenerative changes, diabetes mellitus is seen in a simpler or purer form in children than in adults; in most instances it can be considered simply a metabolic disturbance. The earliest record of infantile diabetes was made by Rollo in 1789, and the first authentic report in an infant under one year of age was published in 1850. Up to 1947, a total of fifty-eight cases were reported.[1, 2] The incidence of diabetes in the pediatric age group has been estimated at 5 to 8 per cent of all cases. White's series[3] showed only 0.5 per cent occurring before one year of life. Only four patients under two years of age with diabetes mellitus have been admitted to the Children's Hospital, Washington, D. C. in the past thirty years. There appears to be no strong sex factor although Chute[4] in his survey on juvenile diabetes indicated a higher incidence in males. Despite the fact that there is a strong racial tendency for this disease in adults, our statistics would indicate that juvenile diabetes is not more common in Jewish children. The concensus is that diabetes is transmitted as a recessive factor.

Juvenile diabetes is attended by a high incidence of coma and death, and diabetic acidosis is a medical emergency of the first order. Because of these facts, the diagnosis should be established promptly and therapy instituted immediately. Recovery from diabetic coma is directly related to the length of time during which it persists before treatment is started, and to the severity of the accompanying acidosis. At this time, a delay of even a few hours in instituting therapy may mark the difference between recovery and death.

Usually, the classical symptomatology is present in juvenile diabetes. This includes polyuria, often with bed-wetting; polydipsia; polyphagia, weight loss; and weakness. Less classical symptoms may be present, e.g., persistent enuresis, superficial skin infection, pruritis, fluctuations in visual acuity, frequent respiratory infections, irritability, listlessness, and crystalline deposits on the diapers. The disease gives a rather clear-cut picture in children. The failure of a physician to make a diagnosis usually can be laid to the fact that diabetes mellitus in childhood is relatively rare. A positive diagnosis is established best by means of blood sugar determinations.

If treated early and adequately, complete control of the disease can be obtained. On the other hand, the longer the disease remains out of control, the more difficult it becomes to attain and maintain complete control. Insulin is required in the treatment of all diabetic children.

The following case is reported because of the age of the patient, the apparent rapidity of onset of symptoms, the high blood sugar when the diagnosis was made, and the rapid response to treatment.

CASE REPORT

L. S., an eighteen-month old white female infant, was born on July 18, 1948. Her delivery was reported as normal and the birth weight was recorded at 6 pounds and 4 ounces. Her stay in the hospital was uneventful, and she was discharged on the seventh post-natal day. The past history and family history were non-contributory. There was no evidence of diabetes mellitus on either the maternal or paternal sides of the family.

On January 19, 1950 the child was admitted to the Children's Hospital with a history of having been perfectly well until two days prior to admission when she vomited, developed fever, and manifested an increased desire for liquids. She was seen by one of us (J. A. W.), and a right otitis media was found. Penicillin was administered, and the family was advised to increase the child's fluid intake by mouth. Shortly thereafter her temperature rose to 103.0 F. and she became markedly dehydrated and dyspneic. She was admitted to the hospital for diagnosis and treatment. Her weight prior to this illness had averaged 21 pounds.

Physical examination on admission revealed a well developed, well nourished, white female infant who was semi-comatose, dehydrated, and having Kussmaul's type of breathing. Examination of the blood revealed a hemoblogin content of 12.5 grams per 100 cubic centimeters; 4,000,000 red blood cells; and 7,000 white blood cells with 53 per cent polymorphonuclear leukocytes (1 per cent immature forms), and 47 per cent lymphocytes. Routine urinalysis disclosed glycosuria and acetonuria. The blood sugar was found to be *1,500 milligrams per 100 milliliters* (Folin-Wu). This was verified by repeating the examination. The carbon dioxide-combining power was 15 volumes per cent.

Treatment was begun immediately with 50 units of regular insulin followed by another 50 units within two hours (both being given subcutaneously), and 500 milliliters of lactate-Ringer solution intravenously. Blood sugar estimations were made at intervals during the acute phase and were recorded as follows:

Admission: 1. 5:30 P.M. 1-19-50, 1500 milligrams per 100 milliliters.
2. 8:30 P.M. 1-19-50, 520 milligrams per 100 milliliters.
3. 10:30 P.M. 1-19-50, 335 milligrams per 100 milliliters.
4. 8:00 A.M. 1-20-50, 140 milligrams per 100 milliliters.

By the following morning (12 hours after admission), the patient had received a total of 100 units of regular insulin and 4 units of protamine zinc insulin. Five-hundred milliliters of fluid had ben administered intravenously. Acetone and diacetic acid disappeared from the urine within fifteen hours after institution of therapy. Fruit juices and skimmed milk not exceeding 4 ounces every four hours by mouth were begun shortly after completion of the parenteral therapy; these were taken eagerly by the patient. After twelve hours, the oral feedings were increased to 8 ounces of skimmed milk or 8 ounces of fruit juice every four hours with a free allowance of

water between feedings. Following this, the skimmed milk was replaced by broth, rice, or junket.

After the acute phase, fluids were kept at a minimum of 1,500 milliliters per twenty-four hour period. Glycosuria was controlled with from 2 to 10 units of unmodified insulin daily with an addition of 4 units of protamine zinc insulin. One week after admission to the hospital the patient was put on a 1,200 calorie diet. This was covered by the administration of insulin determined by capillary blood sugars which were performed three times a day. Penicillin was given during the entire period of hospitalization.

While under therapy in the hospital a bronchitis and a mild case of diarrhea occurred, which were controlled by symptomatic treatment. During the course of regulation, the patient experienced two episodes of hypoglycemia which were treated by the administration of glucose solution intravenously. She was discharged on February 3, 1950.

At the time of writing, the patient is 2.5 years of age, weighs 33 pounds, and is 34.5 inches tall. Her dietary prescription calls for 110 grams of carbohydrate, 50 grams of protein, and 55 grams of fat for a total of 1135 calories per day. She receives 7 units of protamine zinc insulin and 8 units of unmodified insulin daily at breakfast. Her growth and development have been normal.

DISCUSSION

This patient had the highest blood sugar that the clinical laboratory at this hospital has ever reported. Joslin et al[5] reported twenty-four cases in which the blood sugars were over 1,000 milligrams per 100 milliliters; these authors quote a number of other patients with extremely high blood sugars, e.g., Lawrence's[6] patient with a determination of 2,060 milligrams. We are aware that the amount of circulating blood sugar does not determine the condition of the patient; the degree of acidosis and dehydration is of much greater importance.

The therapeutic regimen was aimed at supplying the lack of insulin, hydrating the patient with restoration of fixed base, and combating the infection. Considering the weight of the patient, the amount of insulin given when compared with an adult was equivalent to between 500 and 1,000 units and the fluids to between 3 and 5 liters. The lactate-Ringer solution supplied the various needed electrolytes, including sodium and potassium. The response of the patient to therapy was dramatic, and within a few hours she avidly accepted fluids by mouth. The rapid response and the successful outcome of the treatment given was due in part to the early recognition of the diabetes and ketosis plus the fact that we were dealing with an individual whose organs were undamaged by previous illnesses. This is not the case in the treatment of diabetic ketosis in the adult.

SUMMARY

The case of an eighteen-month old female with diabetic coma with a blood sugar of 1,500 milligrams per 100 milliliters and carbon dioxide of 15 volumes per cent is reported.

A rapid and satisfactory response was obtained following the prompt administration of 100 units of insulin, adequate amounts of fluid, electrolytes, and antibiotics.

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